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THE SYNTHESIS  
OF  
SUBSTANCES ALLIED TO EPINEPHRINE

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(From the Transactions of the Chemical Society, 1905)



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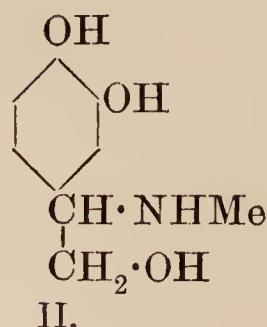
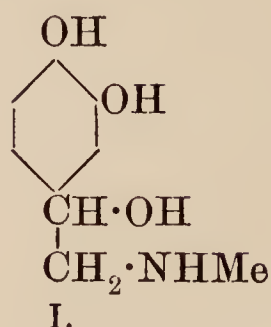
LONDON, S.E.



CII.—*The Synthesis of Substances Allied to  
Epinephrine.*

By GEORGE BARGER and HOOPER ALBERT DICKINSON JOWETT.

IN a previous communication (Trans., 1904, 85, 192) it was shown by one of us that the constitution of epinephrine (adrenaline), the active principle of the suprarenal gland, might be represented by one of the two following formulæ :



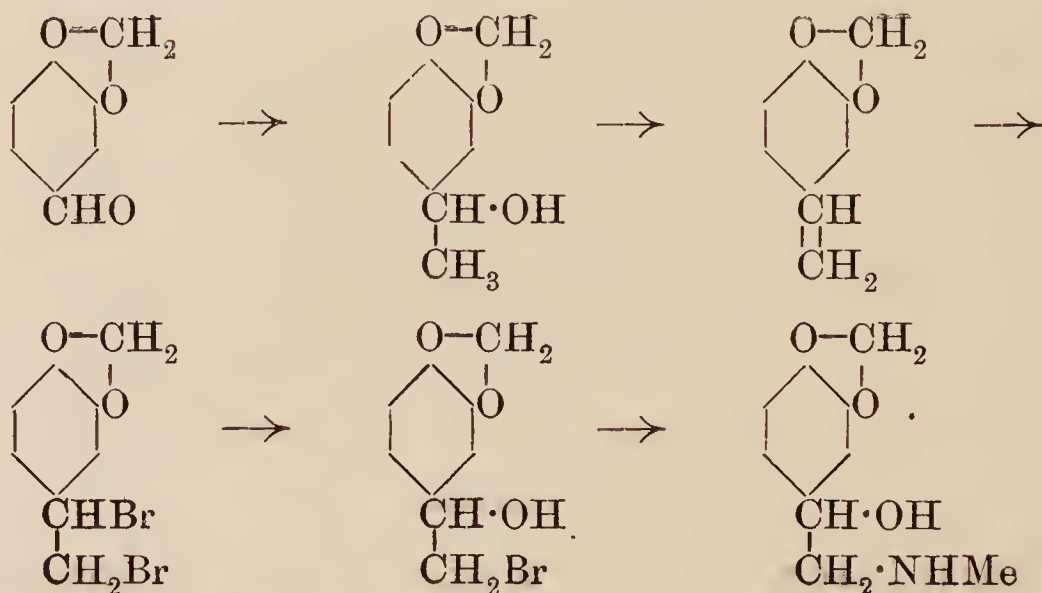
of which I was regarded as the more probable.

These views have since been confirmed by the work of Pauly (*Ber.*, 1904, **37**, 1387), Stolz (*Ber.*, 1904, **37**, 4149), and Friedmann (*Beitr. chem. Physiol. Path.*, 1904, **6**, 92), although the first-named author prefers formula II.

Although we have been unable to synthesise a substance having the constitutional formula I, we have obtained its methylene and dimethyl ethers having the formulæ  $\text{CH}_2\text{:O}_2\text{:C}_6\text{H}_3\text{:CH(OH)\cdot CH}_2\text{:NHMe}$  and  $(\text{CH}_3\text{O})_2\text{:C}_6\text{H}_3\text{:CH(OH)\cdot CH}_2\text{:NHMe}$  respectively. As all attempts to isolate the corresponding dihydroxy-base by the decomposition of the ethers were unsuccessful, we desire to give an account of the synthesis and the properties of the compounds prepared.

The synthesis was carried out as follows: an aldehyde, either piperonal or methylvanillin, was treated with magnesium methyl iodide and thus converted into the secondary alcohol, which, by loss of water, yielded the corresponding styrene. By the addition of bromine to this substance, the dibromide was formed, which by treatment with aqueous acetone yielded the bromohydrin, this product being then condensed with methylamine and the required base thus produced.

The stages in the synthesis may be represented in the case of piperonal as follows:



The constitution of the base produced was proved by its oxidation to piperonylic or veratric acid respectively. Although we were unable to isolate the dihydroxy-base, indications of the formation of a substance having the chemical and physiological properties of epinephrine were



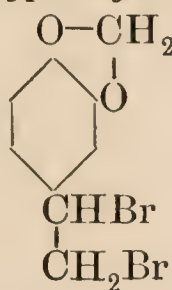
obtained by the action of dilute hydrochloric acid at  $150^{\circ}$  on the methylene ether.

On attempting to carry out this synthesis with vanillin and protocatechuic aldehyde, it was found that these substances did not react with magnesium methyl iodide to give the required styrene. Consequently the synthesis could not be conducted on these lines.

Mameli (*Gazzetta*, 1904, 34, [i], 358) has described a dibromide resulting from the action of bromine water on the styrene, but as this was not identical with the dibromide isolated by us, we repeated his experiments and found that the dibromide described by him is really a bromodihydrin,  $\text{CH}_2:\text{O}_2:\text{C}_6\text{H}_2\text{Br}\cdot\text{CH}\cdot\text{OH}\cdot\text{CH}_2\text{Br}$ . We also obtained this compound from the dibromide,  $\text{CH}_2:\text{O}_2:\text{C}_6\text{H}_3\cdot\text{CHBr}\cdot\text{CH}_2\text{Br}$ , by two distinct methods.

### EXPERIMENTAL.

*$\alpha$ -3 : 4-Methylenedioxyphenyl- $\alpha\beta$ -dibromoethane,*

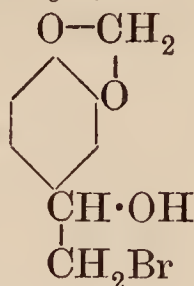


This substance was obtained from the corresponding styrene, which was prepared from piperonal according to the method described by Klages (*Ber.*, 1903, 36, 3595). In order to eliminate water from the secondary alcohol, it was found preferable to convert it first into the chloride, and then remove the elements of hydrogen chloride with pyridine.

3 : 4-Methylenedioxystyrene (20 grams) was dissolved in 20 c.c. of carbon disulphide, and to this a solution of bromine in carbon disulphide (1 gram per c.c.) was gradually added until a faint yellow colour was produced, the liquid being kept cool during the operation. A white, crystalline solid separated, which was collected and washed successively with carbon disulphide and light petroleum. It was recrystallised from carbon disulphide solution by the addition of light petroleum, and thus obtained in white, acicular crystals which melted at  $82-83^{\circ}$ .

0.1598 gave 0.1962 AgBr. Br = 52.2.

$\text{C}_9\text{H}_8\text{O}_2\text{Br}_2$  requires Br = 51.9 per cent.

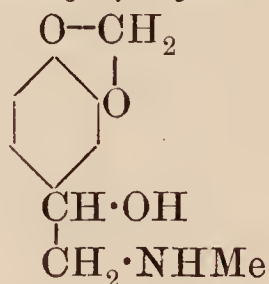
*α-3 : 4-Methylenedioxyphenyl-β-bromo-α-hydroxyethane,*

The dibromide was converted into the corresponding bromohydrin by dissolving it in acetone and then adding water to the acetone solution (compare Auwers and Miller, *Ber.*, 1902, **35**, 114); the liquid was left overnight and the acetone removed by evaporation, when the residue, together with the crystals which had separated, was extracted with ether, the ethereal solution washed with water and distilled. The final residue, which solidified, was recrystallised from hot dilute alcohol, the substance being thus obtained in long, acicular crystals which melted at 107—108°.

0.1758 gave 0.2872 CO<sub>2</sub> and 0.058 H<sub>2</sub>O. C = 44.5 ; H = 3.7.

0.1229 „ 0.0923 AgBr. Br = 32.0.

C<sub>9</sub>H<sub>9</sub>O<sub>3</sub>Br requires C = 44.1 ; H = 3.7 ; Br = 32.6 per cent.

*β-3 : 4-Methylenedioxyphenyl-β-hydroxyethylmethylaniline,*

This substance was prepared by dissolving 4.9 grams of the bromohydrin in alcohol, adding 10 c.c. of an aqueous solution of methylaniline (33 per cent.), and heating the mixture on a water-bath in a reflux apparatus for an hour. The alcohol was then distilled off, the residue dissolved in dilute hydrochloric acid, and extracted with ether to remove any unchanged bromohydrin.

The acid aqueous liquid was next rendered alkaline with sodium carbonate, evaporated to dryness, and the residue extracted with absolute alcohol; the alcoholic solution, after drying with potassium carbonate, left on evaporation a syrupy residue which could not be crystallised. The only crystalline salt obtained was the *picrate*, C<sub>10</sub>H<sub>13</sub>O<sub>3</sub>N, C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub>, which was prepared by dissolving the syrupy base in dilute hydrochloric acid and adding a small quantity of an aqueous solution of picric acid. The liquid was decanted from the yellow oil which separated, and an excess of picric acid added. The



crystalline yellow substance, which slowly separated, was recrystallised, first from alcohol, and finally from water, being thus obtained in rosettes of yellow, acicular crystals melting at  $178^{\circ}$ .

0.1142 gave 0.189  $\text{CO}_2$  and 0.0408  $\text{H}_2\text{O}$ .  $\text{C} = 45.1$ ;  $\text{H} = 4.0$ .

0.0826 ,, 10.2 c.c. nitrogen at  $22^{\circ}$  and 765 mm.  $\text{N} = 13.7$ .

$\text{C}_{16}\text{H}_{16}\text{O}_{10}\text{N}_4$  requires  $\text{C} = 45.3$ ;  $\text{H} = 3.8$ ;  $\text{N} = 13.2$  per cent.

The *platinichloride*, prepared from the base in the usual way, was obtained as a yellow, amorphous powder having no sharp melting point; the base employed in its production was obtained from the pure picrate by decomposition with potassium hydroxide and extraction with chloroform.

0.0686 gave 0.0166 Pt.  $\text{Pt} = 24.2$

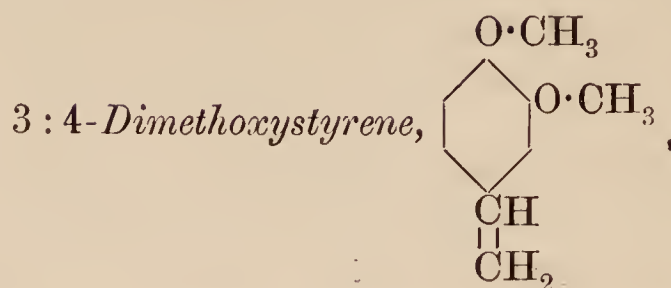
$(\text{C}_{10}\text{H}_{13}\text{O}_3\text{N})_2, \text{H}_2\text{PtCl}_6$  requires  $\text{Pt} = 24.4$  per cent.

When the base was oxidised with potassium permanganate at the ordinary temperature and the product worked up in the usual way, crystals of piperonylic acid (m. p.  $227^{\circ}$ ) were isolated, thus proving the constitution of the base. An aqueous solution of the hydrochloride (2 per cent.) has a very slight physiological action, 0.02 gram, when injected into the jugular vein of a cat, producing a very slight rise (20 mm.) of blood pressure.

A number of experiments were made, both with the bromohydrin and the base, in order to decompose the ether and obtain the corresponding dihydroxy-derivative, but without success. When the base was heated with dilute hydrochloric acid at  $150$ — $160^{\circ}$  for 6 hours, a solution was obtained which gave the catechol reaction with ferric chloride and sodium carbonate, and in very dilute solution gave a pink coloration with ammonia, rapidly turning brown, but no crystalline base could be isolated.

This solution, when injected into the jugular vein of a cat, gave a very marked rise of blood pressure, similar in some respects to that produced by epinephrine, but the amount of active substance present, if it was epinephrine, must have been very minute (approximately 0.005 gram from 2 grams of methylene ether).

On boiling the liquid with alkali and again testing, it was found to have lost its physiological action.

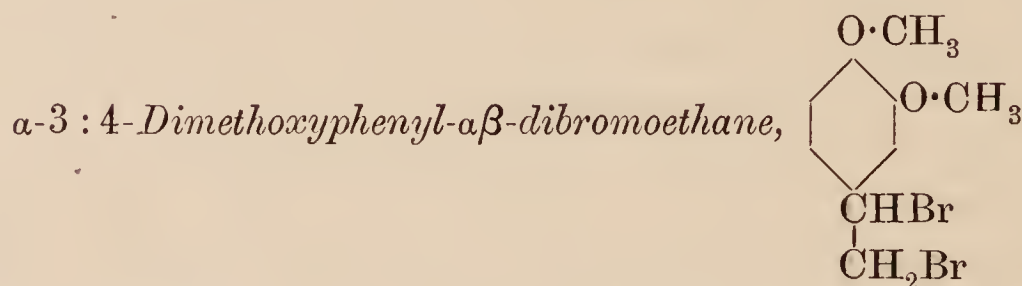


This substance was prepared in a similar manner to the corresponding piperonyl compound by acting on methylvanillin with magnesium methyl iodide, and by withdrawing the elements of water by distillation from the secondary alcohol produced. The crude product distilled between  $135^{\circ}$  and  $170^{\circ}$  under 12 mm. pressure, but after several fractionations a liquid was obtained which boiled at  $120\text{--}125^{\circ}$  under 10 mm. pressure and proved on analysis to be the styrene.

0.1694 gave 0.4508  $\text{CO}_2$  and 0.1136  $\text{H}_2\text{O}$ .  $\text{C} = 72.6$  ;  $\text{H} = 7.4$ .

$\text{C}_{10}\text{H}_{12}\text{O}_2$  requires  $\text{C} = 73.2$  ;  $\text{H} = 7.3$  per cent.]

The higher fraction consisted chiefly of methylvanillin.



This compound was prepared by the addition of bromine to the styrene by using ether as the solvent by a method similar to that employed in the case of the corresponding piperonyl compound ; it was obtained in white, acicular crystals which were purified by recrystallisation from benzene solution with the addition of light petroleum. The crystals melted at  $102^{\circ}$ .

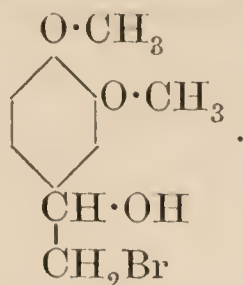
0.1654 gave 0.1932  $\text{AgBr}$ .  $\text{Br} = 49.7$ .

$\text{C}_{10}\text{H}_{12}\text{O}_2\text{Br}_2$  requires  $\text{Br} = 49.4$  per cent.

The yield of dibromide, which was 18 per cent. of the methylvanillin employed, was much smaller than in the case of the corresponding piperonyl compound.



$\alpha$ -3 : 4-Dimethoxyphenyl- $\beta$ -bromo- $\alpha$ -hydroxyethane,



This bromohydrin was prepared from the dibromide by the action of aqueous acetone ; it formed long, acicular crystals, soluble in alcohol, ether, benzene, or carbon disulphide, but insoluble in water or light petroleum ; it recrystallised most readily from carbon disulphide and melted at 68°.

0.1467 gave 0.1069 AgBr. Br = 31.0.

$\text{C}_{10}\text{H}_{13}\text{O}_3\text{Br}$  requires Br = 30.7 per cent.

The bromohydrin was converted into the methylamino-base by the method employed in the case of the piperonyl compound, but the product could only be obtained as a syrup which could neither be crystallised nor converted into any crystalline salt. When oxidised with potassium permanganate, it yielded veratric acid, melting at 179°.

A 2 per cent. solution had a similar physiological action to the corresponding piperonyl compound. When treated with dilute hydrochloric acid for 6 hours at 150—160°, the resulting liquid gave no catechol reaction with ferric chloride ; the ether, therefore, had not undergone hydrolysis.

*Composition of Mameli's Piperonyldibromide.*—This substance was prepared according to the directions given by Mameli (*loc. cit.*), by the action of bromine water on the styrene. In addition to the compound described by him, a considerable amount of the bromohydrin (m. p. 108°) was obtained. The substance was twice crystallised from benzene and twice from alcohol ; it then melted at 158° (Mameli gives 160°).

The same compound was produced by treating the bromohydrin with bromine water in direct sunlight. The yield was 60 per cent. of the theoretical.

0.1425 gave 0.1661 AgBr. Br = 49.6.

0.1442 „ 0.168 AgBr. Br = 49.6.

$\text{C}_9\text{H}_8\text{O}_3\text{Br}_2$  requires Br = 49.4 per cent.

Mameli's formula,  $\text{C}_9\text{H}_8\text{O}_2\text{Br}_2$ , requires Br = 51.9, and he found Br = 51.2 per cent. The results of the analyses together with the method of preparation, by directly brominating the bromohydrin, prove that the substance described by Mameli is not the dibromide but the dibromohydrin. This compound was also obtained in small

amount by the action of phosphorus pentachloride on the dibromide (m. p.  $82^{\circ}$ ) in the attempt to split off the methylene group by the method which Fittig and Remsen used in the preparation of proto-catechuic aldehyde from piperonal (*Annalen*, 1871, 159, 148). The substance melted at  $157-158^{\circ}$ , and when mixed with an equal quantity of the dibromohydrin prepared as previously described, the melting point remained unchanged.

0.1355 gave 0.1681  $\text{CO}_2$  and 0.0308  $\text{H}_2\text{O}$ .  $\text{C} = 33.8$  ;  $\text{H} = 2.5$ .

0.1143 „ 0.1306 AgBr.  $\text{Br} = 48.6$ .

$\text{C}_9\text{H}_8\text{O}_3\text{Br}_2$  requires  $\text{C} = 33.3$  ;  $\text{H} = 2.5$  ;  $\text{Br} = 49.4$  per cent.

The formation of the dibromohydrin by phosphorus pentachloride is explained by the liberation of bromine which takes place in the first stage of the reaction, and the subsequent formation of the bromohydrin by the action of water on the halogen in the  $\alpha$ -position.

Attempts were made also to prepare the styrene by distillation of the calcium salts of the corresponding methylenedioxy-cinnamic acid (compare Tiemann and Will, *Ber.*, 1881, 14, 967). The product obtained was undoubtedly the styrene, as the dibromide was isolated, but the yield was so small (3 per cent.) that this method of preparation had to be abandoned.

The necessary physiological experiments in connection with this inquiry were performed by Dr. H. H. Dale, to whom we wish to tender our best thanks.

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